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## Posttranslational Modifications in Mitochondria: Protein Signaling in the Powerhouse

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### Abstract

There is an intimate interplay between cellular metabolism and the pathophysiology of disease. Mitochondria are essential to maintaining and regulating metabolic function of cells and organs. Mitochondrial dysfunction is implicated in diverse diseases, such as cardiovascular disease, diabetes and metabolic syndrome, neurodegeneration, cancer and aging. Multiple reversible post-translational protein modifications are located in the mitochondria that are responsive to nutrient availability and redox conditions, and which can act in protein-protein interactions to modify diverse mitochondrial functions. Included in this are physiologic redox signaling via reactive oxygen and nitrogen species, phosphorylation, *O*-GlcNAcylation, acetylation, and succinylation, among others. With the advent of mass proteomic screening techniques, there has been a vast increase in the array of known mitochondrial post-translational modifications and their protein targets. The functional significance of these processes in disease etiology, and the pathologic response to their disruption, are still under investigation. However, many of these reversible modifications act as regulatory mechanisms in mitochondria and show promise for mitochondrial-targeted therapeutic strategies. This review addresses the current knowledge of post-translational processing and signaling mechanisms in mitochondria, and their implications in health and disease.

### Keywords

mitochondria; metabolism; post-translational modification; acetylation

### Introduction

Abnormal cellular metabolism and pathology of human disease are intimately linked[1]. Mitochondria are an integral component of normal cellular function, and are central to

maintaining and regulating nutrient flow through metabolic pathways. Mitochondrial dysfunction itself is associated with a number of diseases, including cardiovascular disease, diabetes and the metabolic syndrome, neurodegenerative diseases, cancer and aging[2–7]. Hereditary mitochondrial disorders result in multi-organ dysfunction, signifying the importance of mitochondrial function across tissue types. Because mitochondria provide the vast majority of ATP for cellular activity, mitochondrial dysfunction likely plays a central role in disordered cellular metabolism, thus implicating it as an important pathologic contributor [8–11].

Recently, the discovery that reversible post-translational modifications of proteins are involved in regulating core metabolic processes has generated a tremendous amount of interest [12–17]. It is well known that mitochondrial proteins can undergo post-translational protein modifications similar to nuclear and cytoplasmic proteins. The discovery and knowledge of the mechanisms of mitochondrial protein modifications, and identification of novel target proteins, has exploded recently with the advent of mass spectrometry and analysis capabilities. From this, it is clear that post-translational modifications in mitochondria are abundant and diverse, and that many of these modifications alter mitochondrial function (Table 1) [18].

Post-translational protein modifications typically provide for intra- and inter-cellular signaling and regulation of chemical networks within the cell. As such, many mitochondrial post-translational modifications have been found to be involved in signal transduction pathways modulating mitochondrial energy generation, apoptosis, autophagy, metabolism, and tissue response to ischemic injury. Due to the vast array of post-translational mechanisms and targets, this is not a comprehensive review, and is not meant to contain a complete list of post-translational modification and target protein in the mitochondrial milieu subjected to modification. We will focus our discussion on the main post-translational modifications currently characterized in mitochondria, the mechanism by which they are considered to influence cellular metabolism and function, and their functional relevance to human disease.

## Phosphorylation

One of the oldest known signaling mechanism used by mitochondria to regulate metabolism is targeting metabolic proteins for reversible phosphorylation. In the 1970s, the activity of pyruvate dehydrogenase (PDH) was found to be modulated by a phosphorylation reaction by a PDH-specific kinase and phosphatase to activate or inactive the enzymatic activity in response to cellular energy status[19]. More recently, however, an increasing number of phosphorylated substrates have been identified with diverse roles within mitochondria. The majority of phosphorylation events in the mitochondria are via Src-kinases, non-receptor tyrosine kinases that act by phosphorylating tyrosine residues on protein substrates [17, 20, 21].

Mitochondrial ATP production, generated by OXPHOS via the components of the electron transport chain (ETC), is regulated by reversible phosphorylation (see Figure 1 for a review of the ETC). Phosphorylation of ETC Complex I (CI) subunit NDUFB10 decreases its

activity, while phosphorylation of NDUSF4 increases its activity [22–24]. Complex III (CIII) subunits I and II are reversibly phosphorylated by Src-kinases that decreases the activity of CIII. The Rieske protein of CIII is also reversibly phosphorylated, although with indeterminate effect [25, 26]. Complex IV (CIV) contains multiple sites of reversible phosphorylation with varying effects. CIV subunit IV-1(CIV-I) and IV (CIV-IV) are phosphorylated by protein kinase A (PKA), which increases activity of CIV [27, 28]. Phosphorylation of CIV subunit II (CIV-II) by Src-kinases increases CIV activity [26, 29], while phosphorylation of CIV-II by EGFR decreases CIV activity [30, 31], and phosphorylation of CIV-II by ERBB2 decreases mitochondrial respiration and increases glycolysis [31]. Finally, phosphorylation of Complex V (CV or ATP synthase), the enzyme responsible for harnessing the energy in the electrochemical gradient to synthesize ATP, by Src-kinases decreases its activity [26, 32].

Phosphorylation of proteins in the mitochondria also acts to mediate cell death signals. Phosphorylation of the outer mitochondrial membrane protein, voltage-dependent anion channel (VDAC) up-regulates its expression and induces cellular apoptosis [33]. Phosphorylation signaling cascades have also been implicated in controlling mitochondrial permeability transition pore (mPTP) mediated apoptosis [32].

The relevance of mitochondrial protein phosphorylation in disease is illustrated by its role in cardiovascular events. For instance, the mitochondrial protein STAT3 is involved in cellular respiration. Phosphorylation of STAT3 in response to cardiac ischemia and reperfusion was demonstrated to be important in maintaining ETC CI and CII respiratory activity [34]. Increased phosphorylation in ischemic post-conditioning improved CI respiration and inhibited permeability transition pore opening, and was associated with a reduction in infarct size [35, 36].

## Redox signaling

For many years, oxidative modification in the cell has been considered detrimental to cellular function. Recently, it has become clear that oxidative reactions play a fundamental role in cellular response to redox balance to influence protein-protein interactions and cellular signaling networks. In fact, under physiologic conditions, redox-active molecules exert reversible oxidative post-translational modifications to facilitate signal transduction and modulate cellular function in response to the redox state of the cell [37–42]. Redox-related post-translational modification used in cellular signaling warrants its own review, and indeed, this topic has been comprehensively reviewed recently [40, 43]. Here, we will focus on mitochondrial reversible post-translational modifications that are used as protein signaling with implications in human disease and pathology.

Redox reactions are central to mitochondrial mechanisms of nutrient respiratory metabolism and OXPHOS. In a healthy cell, the redox state is kept carefully in check by counterbalancing reactive oxygen (ROS) or nitrogen species (RNS) production by neutralization with antioxidant defense mechanisms. However, perturbations in the normal redox balance results in accumulation of ROS and RNS leading to oxidative stress and

cellular damage through generation of the highly reactive and toxic  $\text{OH}^-$ , and  $\text{ONOO}^-$ , causing irreversible protein modifications.

Physiologic levels of ROS (in the form of  $\text{O}_2^-$  and  $\text{H}_2\text{O}_2$ ) act as signaling molecules in the mitochondria, for example, by reacting with protein thiols to form reversible modifications on target proteins. Such oxidative modifications can act as messengers to signal changes in redox balance and allow the cell to modulate metabolism accordingly[44]. This has physiologic significance in the cardiovascular system, where mitochondrial production of  $\text{H}_2\text{O}_2$  couples myocardial oxygen consumption to coronary blood flow [45]. Redox-related protein modifications include S-oxidation (sulfenylation and sulfinylation), S-nitrosylation, and S-glutathionylation.

Nitrosylation is a post-translational modification in which reactive nitrogen species (RNS) perform selective modification of protein cysteine residues to form S-nitrosocysteine (S-nitrosylation of cysteine residues). These reversible reactions occur under normal physiologic redox conditions in the cell and act as signals to modulate a diverse array of cellular function[18, 46–50]. A recent mass spectrometry-based approach to identifying nitrosylated proteins in the mouse revealed that over half of the nitrosylated proteins identified in the heart, and approximately a quarter in the brain, kidney, liver, lung, and thymus, were localized to mitochondria [51]. This reveals the heavy use of nitrosylation protein signaling in mitochondrially-dependent, metabolically active tissues.

In the mitochondria, nitric oxide (NO) can form nitrosyl or nitrite adducts with CIV to act directly as a competitive and reversible inhibitor to regulate mitochondrial respiration in response to fluctuations in redox and energy state. NO and oxygen compete for binding to the active center of CIV. In relative hypoxia, NO binding inhibits CIV activity and slows the rate of OXPHOS and ROS production [37, 52, 53]. Similarly, S-nitrosylation of ATP synthase inhibits its activity [46].

Mitochondrial metabolic enzymes that have been identified as targets of nitrosylation include those involved in fatty acid oxidation, including very long chain acyl-coenzyme A (CoA) dehydrogenase (VLCAD), and components of the tricarboxylic (TCA) cycle. VLCAD increases its enzymatic activity in response to S-nitrosylation[51]. Nitrosylation also plays a role in mitochondria-regulated cell death. S-nitrosylation of cyclophilin D, simulating protein modification under low levels of nitric oxide, inhibits opening of the mPTP and prevents induction of apoptosis [54, 55]. Similarly, NO modification of mitochondrial caspase-3 results in inhibition of inducible cell death pathway [56]. These findings have mechanistic implications for protein modifications acting as mediators in cardiomyocyte apoptosis in response to ischemic insult.

Clear pathophysiologic relevance is demonstrated by S-nitrosylation protection from myocardial ischemia-reperfusion injury [57, 58]. Specific mechanisms may involve reversible S-nitrosylation of CI, which was shown to exhibit a cardioprotective effect by reducing infarct size in myocardium exposed to ischemic insult. This resulted in reduction in activity of CI and decreased ROS generation, which would be expected to contribute to the mechanism of cardioprotection [39, 59, 60].

## O-GlcNAcylation

O-linked beta-N-acetylglucosamine (O-GlcNAc) attachment to Ser/Thr residues (O-GlcNAcylation) is a nutrient-sensitive and reversible post-translational protein modification employed in cellular signaling. It is almost as wide spread and varied as phosphorylation, and in fact, phosphorylation and O-GlcNAcylation appear to be intricately linked along multiple cellular pathways and play interrelated roles in pathological states [61–63]. Based on large scale proteomic techniques, the number of known O-GlcNAcylation protein targets has exploded in recent years, with now more than 4000 identified throughout the cell [64].

The enzyme O-GlcNAc transferase (OGT) is responsible for adding O-GlcNAc to target proteins, and the enzyme O-GlcNAcase (OGA) catalyzes its removal. Both an isoform of OGT (mOGT) and OGA have been found in mitochondria, and a specific mitochondrial transporter has been identified that imports the donor substrate (UDP-GlcNAc) [65–67], providing evidence for the functional significance of O-GlcNAcylation as a regulatory PTM in mitochondria. O-GlcNAc mitochondrial protein modification is targeted to enzymes involved in diverse processes from mitochondrial metabolism of the TCA cycle, electron transport chain and lipid metabolism, as well as proteins involved in mitochondrial division and apoptosis signaling [68, 69]. Mounting evidence suggests that the expression and activity of the nutrient-sensitive mOGT is important in regulating mitochondrial metabolism, as well as mitochondrial apoptosis via protein modifications [66, 70–74].

Of particular relevance to how metabolic dysfunction impacts normal post-translational modifications is the effect of prolonged nutrient excess on O-GlcNAcylation. Aberrantly high levels of glucose and fatty acids result in elevations in O-GlcNAcylation, as occurs in diabetes [71]. Increased levels of O-GlcNAcylation in diabetes has been implicated in widespread cellular dysfunction. Specifically, abnormalities in O-GlcNAcylation have been shown to be associated with impaired respiratory activity, decreased ATP content, and lower mitochondrial calcium [71, 73]. While not mitochondria-specific, *per se*, decreased O-GlcNAcylation has shown to improve cardiac function in diabetic mice [75, 76]. This provides evidence that disordered O-GlcNAc protein modification appears to be pathologically relevant to the mitochondrial dysfunction associated with the hyperglycemia of diabetes and its associated complications.

## Lysine Acetylation

Sirtuins are a family of NAD<sup>+</sup>-dependent enzymes that regulate diverse biological functions. There are seven identified sirtuins, sirtuin 1–7, with three located in mitochondria, sirtuin 3–5. Sirtuin 3 (SIRT3) is a deacetylase that responds to cellular energy status and utilizes an “acetylation switch” to modify protein function [77–79]. SIRT3 catalyzes the removal of acetyl groups from lysine side chains. Mitochondria appear to utilize lysine acetylation-deacetylation of proteins to respond quickly to metabolic cues and thus, represents an important post translational mechanism for maintaining normal mitochondrial function and metabolism [79]. While early reports suggested the presence of an acetyltransferase mechanism [80], definitive identification of such a counter enzyme has not been successful. Rather, acetylation appears to be non-enzymatic, and related to acetyl CoA availability and

reactivity in the mitochondrial matrix [81, 82]. Sirtuin 4 (SIRT4) has demonstrated only weak deacetylase activity, and while the primary activity of SIRT4 remains largely uncharacterized, it has been shown to have mono-ADP-ribosylase activity [83, 84]. SIRT5 is discussed below.

SIRT3 targets enzymes that typically activate in response to removal of acetyl groups, and which are important to energy generation and utilization, such as long-chain acyl-CoA dehydrogenase (LCAD) [85, 86], pyruvate dehydrogenase (PDH) [87], acetyl-CoA synthetase 2 (AceCS2) [88], Isocitrate dehydrogenase 2 (IDH2) [89], and ETC complexes I–III and CV (ATP synthase)[90–93], among others important to core metabolic processes (Figure 2) [94–97]. SIRT3 deacetylation has been shown to increase the activity of CI-NDUFA9, CII-SDHA and ATP synthase [90, 91, 98, 99]. Fatty acid metabolism is regulated by deacetylation of AceCS2, which stimulates conversion of acetate into acetyl CoA [88, 100], 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) stimulating ketogenesis [101], and LCAD, stimulating fatty acid oxidation [86]. Malonyl CoA decarboxylase (MCD) is the only known substrate of SIRT4 deacetylase activity. Deacetylation inhibits MCD, thus inhibiting fatty acid oxidation and promoting lipogenesis [102]. Carbohydrate metabolism is regulated by deacetylation of cyclophilin D, releasing hexokinase 2 and causing a decrease in glycolysis [103], and PDH, which activates in response to deacetylation by SIRT3 [104].

SIRT3 also targets proteins that maintain redox balance and provide protection from oxidative damage. Deacetylation of superoxide dismutase 2 (SOD2) increases its activity as a free radical scavenger [105–107]. IDH2 responds to deacetylation with increased metabolic activity in the TCA cycle, and is also associated with protection from oxidative stress-related cell death [89]. Mitochondrial permeability transition pore-mediated apoptosis is also regulated by deacetylation, with deacetylation by SIRT3 inhibiting pore opening[95]. Mitochondrial OGG1 (8-Oxoguanine glycosylase) stabilizes in response to deacetylation by SIRT3 under oxidative stress and protects from intrinsic apoptosis [108].

Particular functional relevance of acetylation post-translational modification is in cardiovascular disease. Given the heart's reliance on functional mitochondrial metabolism due to its constant demand for energy substrates, it is not surprising that SIRT3 is emerging as an important player in cardiovascular disease[109]. For example, SIRT3 has been shown to protect against oxidative stress [110–112], attenuate fatty acid accumulation in the heart [113] and prevent development of stress-induced cardiac hypertrophy [114]. Recent reports demonstrate that mice lacking SIRT3 have mitochondrial dysfunction resulting in myocardial energy loss, develop hypertrophy and fibrosis in response to mechanical stress [115], and are more susceptible to the detrimental effects of ischemia/reperfusion injury [116].

### **Lysine Acylation (Succinylation, Glutarylation, Malonylation)**

Most recently, protein modification by lysine malonylation, succinylation, and glutarylation, and their regulation by the NAD<sup>+</sup>-dependent sirtuin, SIRT5, have gained greater interest. The functional characterization of each of these post-translational modifications is still being investigated. SIRT5 catalyzes deacylation (desuccinylation, deglutarylation and



demalonylation) of mitochondrial proteins, and dynamically regulates these pathways. Lysine succinylation is a conserved and common post-translational modification across tissues [117–119]. Desuccinylation has been implicated in numerous metabolic signaling pathways. The electron transport chain CII subunits, succinate dehydrogenase (ubiquinone) flavoprotein (SDHA), and Succinate dehydrogenase (ubiquinone) iron-sulfur subunit (SDHB), are targets of SIRT5 desuccinylation [117]. Desuccinylation of HMGCS2 (3-hydroxy-3-methylglutaryl-CoA synthase 2) activates its enzymatic activity [118]. PDH is also a target of desuccinylation by SIRT5 that inactivates PDH [117]. ROS regulation is controlled by desuccinylation of SOD1, which increases its activity [120]. Lysine malonylation appears to play a role in glucose metabolism by responding to glucose levels and may regulate glycolytic and gluconeogenic pathways. In liver tissue of mice lacking SIRT5, protein malonylation increased and glycolytic flux was significantly diminished [119], providing evidence for a role of SIRT5 in regulating malonylation. Lysine glutarylation appears to be metabolically regulated through the actions of SIRT5 deglutarylation. Protein glutarylation changes in response to feed-fast states and targets the rate-limiting mitochondrial enzyme in the urea cycle, carbamoyl phosphate synthase 1 (CPS1), with glutarylation inhibiting its activity. CPS1 was also identified as a target for deglutarylation by SIRT5. Taken together, lysine acylation in its early stages of characterization appears to regulate diverse mitochondrial metabolic processes through protein post-translational processing [121].

## ADP-Ribosylation

ADP-ribosylation, or poly(ADP-ribosylation) (PARylation) is a reversible PTM that requires  $\text{NAD}^+$  as a cofactor. The enzymes poly(ADP-ribose) polymerases (PARPs), also known as ADP-ribosyltransferases (ARTs) according to their transferase activity [122], act by cleaving  $\text{NAD}^+$  into nicotinamide (NAM) and ADP-ribose (ADPR) and transferring the ADPR onto select amino acid residues of substrate protein side chains or onto another ADPR. By adding subsequent ADPR units, they can build an ADPR polymer, or poly(ADP-ribose) (PAR), on the target protein. Multiple PARPs have been identified [122], with PARP-1 activity responsible for the majority of PARylation in the cell [123]. PARylation has been well described in the nucleus and cytosol, and nuclear PARylation has a well-defined regulatory role in DNA repair, transcription and cell division [124]. PARPs are activated by DNA and oxidative damage, increased calcium, interaction with phosphorylated ERK2, and reversible acetylation [125–130]. Mechanisms of PARP inhibition include auto-PARylation, phosphorylation by protein kinase C, and sumoylation [131–133]. PARylation in the cell is controlled by the enzymes Poly (ADP-Ribose) glycohydrolase (PARG) and ADP-ribosyl protein hydrolase-3 (ARH-3), which rapidly degrade PAR [134, 135].

Attention has been recently directed at PARylation as an important PTM in regulating mitochondrial function. However, it remains under debate whether there exists a mitochondria-specific PARP and localized mechanism of action, or whether the effects of PARylation is exerted on mitochondrial proteins via nuclear or cytosolic PARP activity (e.g. PARP-1). Recent comprehensive reviews on the role of PARylation in mitochondria have been published [136–138] which discuss the cumulative body of research and ongoing investigation into mitochondria-relevant PARylation.

It is clear that PARP-1 activation and PARylation negatively affect mitochondrial energy metabolism. Interestingly, PARP-1 can travel outside the nucleus and bind to mitochondria, resulting in inhibition of OXPHOS activity and energy depletion, via an interaction with hexokinase [139]. Experimental overexpression of mitochondria-targeted PARP-1 led to increased PARylation of intra-mitochondrial proteins and reduction in mitochondrial respiratory activity and energy depletion [140]. Activation of PARP-1 in cell culture lead to decreased mitochondrial respiration, cellular energy equivalents, mitochondrial membrane collapse and mitochondria-induced cell death, and was reversed with PARP-1 inhibition [141].

Both PARylation and deacetylation rely on NAD<sup>+</sup> metabolism, and PARP activation leads to depletion of NAD<sup>+</sup> [142]. Further, PARPs have been found to be targets of acetylation [130, 143]. Thus, an important consideration is whether there is a metabolic regulatory interaction between PARylation and acetylation [144]. Indeed, recent studies have provided evidence of such an interaction. Activation of PARP-1 in cardiomyocytes and failing mouse hearts resulted in depletion of NAD and inhibition of SIRT1 and lead to cell death [145]. Conversely, deletion of PARP-1 lead to increased NAD<sup>+</sup>, activated SIRT1 and outcome measures consistent with enhanced mitochondrial function in brown adipose and muscle tissue [146]. Blocking PARP-1 in diabetic retinal endothelial cells prevented associated downregulation of SIRT3 and protected the cells from oxidative damage [147].

## Conclusion

The rapid and recent increase in knowledge of protein post-translational processing mechanisms and their known mitochondrial targets has lead to a tremendous amount of new information on the mitochondrial orchestration of cellular energy and metabolism. Certainly, the functional significance of many of these post-translational modifications in the mitochondria in regards to their impact of in the pathophysiology of disease remains under intense investigation. However, it is evident that protein signaling via reversible protein modifications is widely and extensively used in mitochondria to respond to nutrient and redox status. Given the fundamental role of mitochondria in providing energy and regulating metabolic homeostasis of the cell, and the close link between mitochondrial dysfunction and disease, ongoing investigations will likely continue to yield clues to functional significance. Mitochondrial protein modifications continue to show promise for use as modifiable mitochondrial targets for therapies aimed at metabolic regulation.

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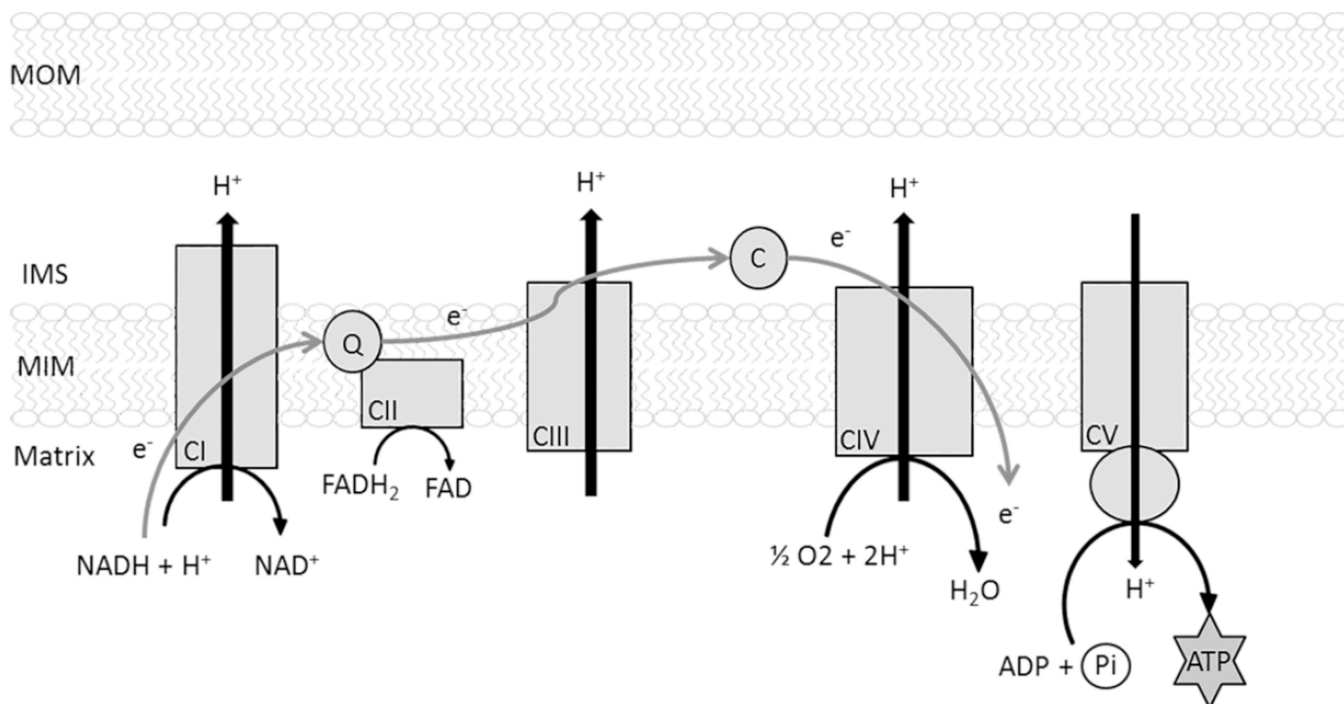
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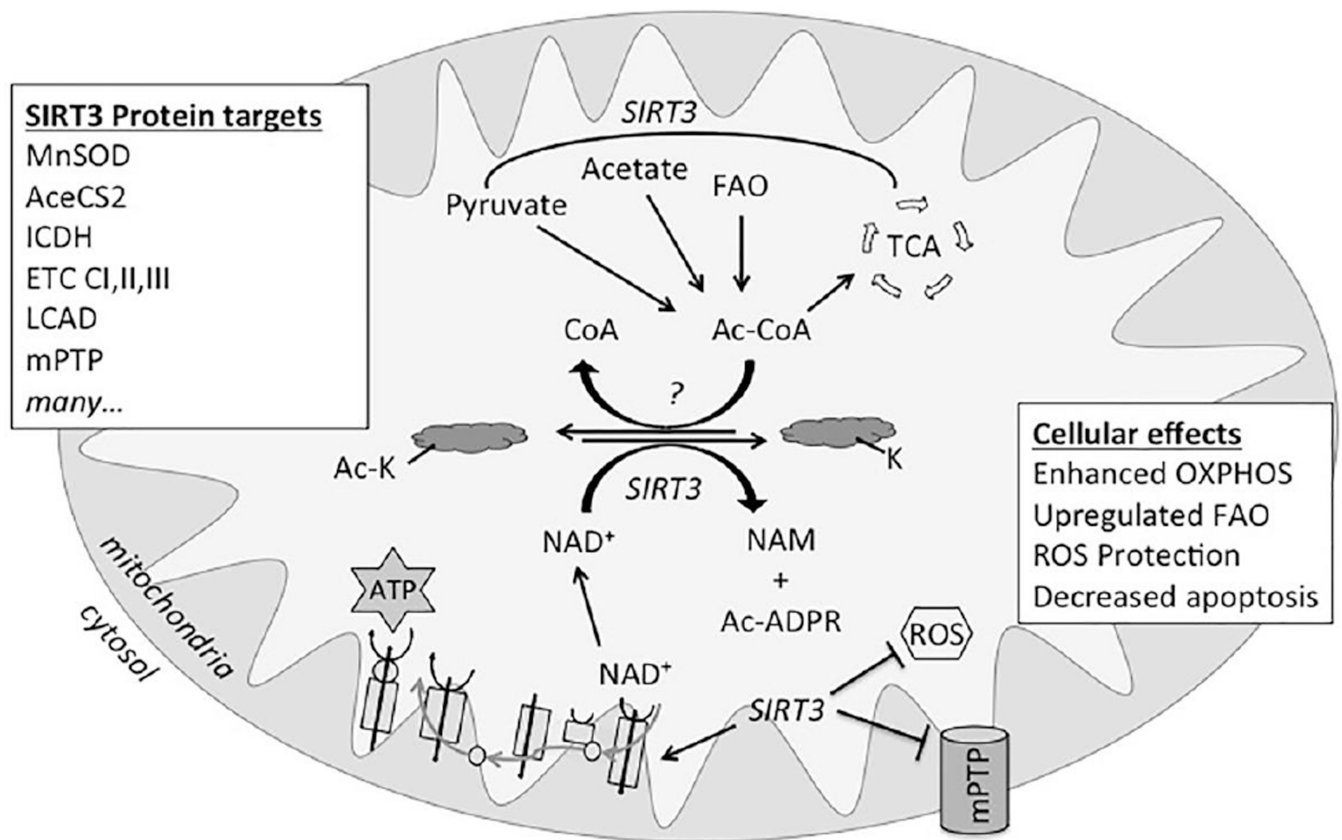


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**Figure 1.**

Overview of oxidative phosphorylation (OXPHOS) enzyme complexes of the electron transport chain (ETC) and flow of electrons through the system coupled to ATP generation (chemiosmotic coupling). Post-translational modification of ETC proteins is an important regulatory mechanism in mitochondria, and is used to respond to changes in metabolism and energy requirements. MOM = mitochondrial outer membrane; IMS = intermembrane space; MIM = mitochondrial inner membrane; CI = NADH dehydrogenase; CII = ubiquinol cytochrome c reductase; CIII = succinate dehydrogenase; CIV = cytochrome c oxidase; CV = ATP synthase; Q = coenzyme Q; C = cytochrome c



**Figure 2.**

Reversible Lysine Acetylation. Mitochondrial protein lysine acetylation is regulated by the NAD<sup>+</sup>-dependent deacetylase, SIRT3. SIRT3 responds to mitochondrial energy and redox state to target proteins that, in turn, signal changes in cellular function. Ac-CoA = Acetyl-CoA; FAO = fatty acid oxidation; ? = no identified acetyltransferase enzyme; Ac-K = acetyl-lysine; K = lysine; NAM = nicotinamide; ADPR = ADP-Ribose; ROS = reactive oxygen species; mPTP = mitochondrial permeability transition pore

Table 1

Select mitochondrial PTMs, their target proteins and regulatory effects.

PTM	Enzyme	Reverse catalyst	Chemical group	Selected targets*	Effects
Phosphorylation	kinase	phosphatase	high energy phosphate	ETC	decreased activity
				<i>CI: NDUFBI0</i>	
				<i>CI: NDUSF4</i>	increased activity
				<i>CIII: subunits 1 and 2</i>	decreased activity
				<i>CIV: multiple sites</i>	decreased and increased activity
				<i>CV</i>	decreased activity
S-nitrosylation	RNS		S-nitrosocysteine	VDAC	induces apoptosis
				GSK-3β	mPTP inhibition, prevent apoptosis
				PDH: E1	inactivation
				<u>ETC</u>	inhibition, reduction in ROS
				<i>CI</i>	
				<i>CIV</i>	inhibition, reduction in ROS
O-GlcNAcylation	OGT	OGA	O-GlcNAc	<i>CV</i>	inhibition, reduction in ROS
				VLCAD	increased activity
				cyclophilin D	mPTP inhibition, prevent apoptosis
				<u>ETC</u>	
				<i>CI</i>	inhibits
				<i>CIII</i>	inhibits
Deacetylation	SIRT3	non-enzymatic	acetyl-CoA	<i>CV</i>	inhibits
				<u>ETC</u>	
				<i>CI-CIII</i>	activates

PTM	Enzyme	Reverse catalyst	Chemical group	Selected targets*	Effects
				LCAD	activates
				HMGCS2	activates
				PDH	activates
				AceCS2	activates
				SOD2	activates
<b>Deacylation</b>					
Desuccinylation	SIRT5		succinyl-CoA	HMGCS2	activates
				PDH	inactivates
Deglutarylation	SIRT5		glutaryl-CoA	SOD1	activates
				CPS1	activates

\* = more targets are known but not listed in some cases; GSK-3β = Glycogen synthase kinase; OGT = O-GlcNAc transferase; OGA = O-GlcNAcase; carbamoyl phosphate synthase 1